Morbidity of radiotherapy
carcinoma prostate

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P.D. Hinduja National Hospital
Mumbai
1. Gastro-intestinal effects (GI)
2. Genitourinary effects (GU)
3. Erectile dysfunction (ED)
Acute GI effects
Acute GI effects - RTOG grade

Grade I
- Increased stool frequency
- Rectal discomfort
- Change in quality of bowel habit
  - No drugs required

Grade II
- Diarrhoea, needs drug
- Mucus discharge, no pads
- Pain rectum, needs drug, occasional narcotic

Grade III
- Diarrhoea, needs I.V.
- Mucus / blood discharge, pads needed
- Abdominal distension

Grade IV
- Sub acute or acute obstruction / fistula / perforation
- GI bleed, needs transfusion
- Abdomen pain / Tenesmus, needs bowel diversion or tube decompression.
Acute GI effects

- Mild effects due to radiation 6 - 37.5 %
- Severe effects, 0 – 10 %, interrupts treatment
- Weekly evaluation 90 – 95 % ≤ grade II
Acute GI effects

- Diarrhea
- Pain
- Urgency
- Constipation
- Bleeding
- Mucous discharge

Acute radiation proctitis
Acute GI effects
IMRT

Grade 0  34%
Grade 1  39%
Grade 2  27%
Grade 3  -

Fig. 2. Evolution of number of patients with acute gastrointestinal toxicity as a function of time. The black bars represent the toxicity during radiotherapy. The white bars represent the toxicity 3 months after the end of radiotherapy. Numbers are presented as percentages (y axis).

De Meerleer et al., IJROBP 2004, 60, 777
**Acute GI effects**

N = 306, GETUG, Multicentre, France, 3DCRT, 70 vs 80 Gy

<table>
<thead>
<tr>
<th>Grade</th>
<th>70 Gy, n=153</th>
<th>80 Gy, n=153</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>42</td>
<td>50</td>
</tr>
<tr>
<td>1</td>
<td>66</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

- GI acute effects 70%
- Increases with increase in CTV
- No treatment interruption

Beckendorf V et al., IJROBP, 2004, 60, 1056
Acute GI effects

Intrarectal balloon, N 100, IMRT 75.8 Gy

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>83%</td>
</tr>
<tr>
<td>Grade I</td>
<td>11%</td>
</tr>
<tr>
<td>Grade II</td>
<td>6%</td>
</tr>
</tbody>
</table>

Teh BS etal. IJROBP, 2001, 49, 705
Acute GI effects

3DCRT (1997 – 2002), 72 Gy/40f, n=51

P.D. Hinduja National Hospital, Mumbai

Rectal Toxicity (RTOG)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>4</td>
</tr>
<tr>
<td>Grade 1</td>
<td>31</td>
</tr>
<tr>
<td>Grade 2</td>
<td>16</td>
</tr>
</tbody>
</table>

Kannan V et al, JCRT, 2005, 1, 34
Acute GI effects, Pathophysiology

Rectal mucosa

- Edema, Hyperemia, Excess Mucus
- Acute inflammatory cells (eosinophil, mast cell) in lamina propria
- Crypt abscess

The severity of histological changes peaks at 2 weeks and improves at 6 weeks despite increase in severity of symptoms
Late GI effects
Late GI effect, RTOG grade

Grade I
- mild diarrhea/cramp
- bowel movement $\leq 5$/day
- slight rectal discharge/bleed

Grade II
- mild diarrhea & colic
- bowel movement $>5$/day
- excess rectal discharge/intermittent bleed

Grade III
- obstruction/bleed requiring surgery

Grade IV
- Necrosis/perforation/fistula
Late GI effects

Symptoms
- Diarrhea
- Pain
- Urgency
- Constipation
- Bleeding
- Mucous discharge

End of XRT
- 1 month
- 5 months
- 10 months
- 15 months
- years after

{ chronic radiation proctitis }
Late GI effect, pathophysiology

- Mucosa: flattened surface epithelium
- Submucosa: myxoid change, edema, hyaline fibrosis, atypical plump fibroblasts
- Vascular changes: atypical endothelial cells, intimal fibrosis, lipid deposition, intraluminal thrombosis, adventitial fibrosis
- Telangiectasia
Late GI effect, Ano-rectal physiology

Manometric study of ano-rectal mucosa shows decreased

- sensory threshold
- maximum tolerated volume
- voluntary squeeze
- basal resting pressure

leading to fecal urgency

Epithelial, vascular, extracellular components and enteric nervous system all contribute to late injury
Late GI effect

Risk factors

1. Presence of anal symptoms prior to treatment
2. Older age
3. Diabetes
4. Acute GI effects
5. Dose/2D/3DCRT
6. Rectal dose volume
7. Anal dose volume
8. IMRT
9. Hypofraction
Late GI effect

Pretreatment presence of GI symptoms increases the risk of post treatment GI morbidity

Borghede G et al, RT&Oncol, 1997, 43,139
Peeters ST et al IJROBP, 2006, 64, 1151
Late GI effect

2. Older age

Older patients have higher risk of grade II rectal bleed

N=171, 3DCRT-64.8 to 81 Gy, T1-T3, MSKCC

Late rectal grade II bleeding patients were slightly older than non-bleeding patients (69.7 vs 68.3)

Skwarchuck MW et al, et al IJROBP, 2000, 47, 103
3. Diabetes mellitus (DM)

**Late GI effect**

N=52, 69Gy at 3Gy/f, PTV-prostate, 4field

- Age
- T stage
- DM
- Dosimetric factors studied

**Only DM was significant for late grade ≥2 toxicity**

Late GI effect

N 1571, T1-T3, 3DCRT / IMRT, 68 – 81 Gy (MSKCC)

<table>
<thead>
<tr>
<th>Acute morbidity</th>
<th>Late morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 2</td>
<td>42 %</td>
</tr>
<tr>
<td>&lt; 2</td>
<td>9 %</td>
</tr>
</tbody>
</table>

acute GI ≥ II, increased late G-II

Zelefsky MJ et al, IJROBP, 2008, 70, 1124
Late GI effect

Prostate cancer, Dose response

9 institutions data

1994-1995, N=1325, T1,2
Median follow-up =5.8 years

8 year PSA DFS = 62%

Dose ≥72Gy : improves outcome

Kupelian P et al, IJROBP, 2005 61, 415
Severe proctitis / necrosis / fistulae / stenosis
- $TD_{5/5}$ 60 Gy for entire rectal circumference
- $TD_{50/5}$ 80 Gy

Minimal late risk with 50 to 60 to posterior rectal wall

Risk of late complication increases with:
1. Post. Rectal wall dose 65-70 Gy
2. Ant rectal wall dose 75 Gy

Emami et al, 1991
Conformal Therapy reduces risk of grade II and III proctitis compared to conventional therapy.

**Late GI effect**

**Standard dose**

Conformal Therapy reduces risk of grade II and III proctitis compared to conventional therapy.

N 225, 2D vs 3D, 64 Gy

Remaining free of ≥ grade II proctitis, 5 years

<table>
<thead>
<tr>
<th>2D</th>
<th>3D</th>
</tr>
</thead>
<tbody>
<tr>
<td>82 %</td>
<td>92 %</td>
</tr>
</tbody>
</table>

RMH, Dearnaley DP, Lancet, 1999, 353, 267

5.2.1. Dose, 2D vs 3D

Nguyen LN et al, Urology, 1998, 51, 991
Sandler HM et al, IJROBP, 1995, 33, 797
Schultheiss TE et al, IJROBP, 1995, 32, 643
Late GI effect

3DCRT (1997 – 2002), 72 Gy/40f, n=51

P.D. Hinduja National Hospital, Mumbai

Rectal Toxicity (RTOG)

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<tr>
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<th>Count</th>
</tr>
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<tbody>
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<td>Grade 0</td>
<td>41</td>
</tr>
<tr>
<td>Grade 1</td>
<td>3</td>
</tr>
<tr>
<td>Grade 2</td>
<td>5</td>
</tr>
</tbody>
</table>

Kannan V et al, JCRT, 2005, 1, 34
Late GI effect

5.3.2. Dose, 3DCRT

Prospective study

3D-CRT, RTOG 9406, 78 Gy, n=218,

Late ≥Grade 2 Rectal complication: 30 – 33%

Michalski JM et al, IJROBP, 2005, 62, 706
5.3.3. Dose, 3DCRT

Prospective study

Fox Chase Cancer Center

n=230, Dose 63-79 Gy

75-76 Gy: Grade 2 - 32%

Hanks GE et al, IJROBP, 1998, 41, 501
Late GI effect

Prospective study

N 1571, T1-T3, 3DCRT, MSKCC

Grade II - 9% at 10 years

<table>
<thead>
<tr>
<th>Dose</th>
<th>Late GI effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>70.2, 3D</td>
<td>7%</td>
</tr>
<tr>
<td>75.6, 3D</td>
<td>18%</td>
</tr>
</tbody>
</table>

Zelefsky MJ et al, IJROBP, 2008, 70, 1124
**Late GI effect**

**Higher dose increases morbidity – 3DCRT**

Prospective randomized study

<table>
<thead>
<tr>
<th>Location</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Late GI Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH Boston, Loma Linda</td>
<td>70.2 GyE</td>
<td>79.2 GyE</td>
<td>8% → 17%</td>
</tr>
<tr>
<td>Zietman AL et al, JAMA, 294, 1233, 2005</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRC RT01, UK</td>
<td>64 Gy</td>
<td>74 Gy</td>
<td>24% → 33%</td>
</tr>
<tr>
<td>Dearnaley DP et al, Lancet Oncol, 2007, 8, 475</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD Anderson Hospital</td>
<td>70 Gy</td>
<td>78 Gy</td>
<td>13% → 26%</td>
</tr>
<tr>
<td>Kuban et al, IJROBP, 2008, 70, 67</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Late GI effect

N=124, 3DCRT, 70 Gy

Rectal volume receiving ≥ 70 Gy ($V_{70}$) was most predictive of grade 2 morbidity

<table>
<thead>
<tr>
<th>$V_{70}$ &lt; 20%</th>
<th>37%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{70}$ ≥20%</td>
<td>61%</td>
</tr>
</tbody>
</table>

van der Laan et al, IJROBP, 2008, 70, 1138
### Late GI effect

#### Rectal dose volume

<table>
<thead>
<tr>
<th>Study</th>
<th>Rectal dose volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vargas et al, 2005</td>
<td>V70 &gt;40%</td>
</tr>
<tr>
<td>Kuban et al, 2003</td>
<td>V70 ≥26%</td>
</tr>
<tr>
<td>Huang et al, 2002</td>
<td>V70 ≥26.2%</td>
</tr>
<tr>
<td>Storey et al, 2000</td>
<td>V70 &gt;25%</td>
</tr>
</tbody>
</table>

Storey NR et al, IJROBP, 2000, 48, 65
6.3 rectal dose volume

Late GI effect

Rectal volume with doses < 60 Gy might be more strongly associated with rectal morbidity

1. At prostate dose 70.2 – 75.6 Gy when 50% isodose encompasses entire rectal volume at isocentre slice – higher grade II bleeding \(^{(1)}\)
2. Grade II or more morbidity for V32 for rectal wall ≥ 80 % \(^{(2)}\)

1. Skwarchuk MW et al, IJROBP, 2000, 47, 103
2. Tucker SL et al, IJROBP 2004, 60, 1589
Late GI effect

1. A new class of NTCP models called “cluster models” have been developed in which spatial distribution of dose to normal tissue (rectum) is taken explicitly into account.

2. The size of rectal wall exposed to doses between 27 and 43 Gy, with cluster model analysis, was found to be significantly associated with late GI effect

Tucker SL et al IJROBP 2006, 64, 1255
Late GI effect

Endorectal balloon (ERB)

1. Reduced rectal volume exposed to >40Gy
2. Reduction in late rectal mucosal changes
3. Reduction in late rectal toxicity

ERB pushes the lateral and posterior wall away from high dose region

Air filled ERB may cause additional dose reduction to superficial anterior rectal mucosa because of dose build up effect without under dosing prostate gland

6.5 rectal dose volume

Th. van Lin ENJ et al, IJROBP, 2007, 67, 799
**Late GI effect**

Incontinence requiring pads

- mean anal wall dose > 33 Gy
- no correlation to rectal dose

Late rectal bleed - correlates with anorectal V65 dosimetry (relative wall volume receiving 65 Gy)
- V65 < 30% - reduced risk of bleed
- V65 increase from 19 to 43% bleed 1 to 9%

Peeters ST et al IJROBP, 2006, 64, 1151

7. Anal dose volume
8.1. IMRT

Late GI effect

N 1571, T1-T3, 3DCRT / IMRT, 68 – 81 Gy (MSKCC)

Grade II 9% at 10 years

<table>
<thead>
<tr>
<th></th>
<th>IMRT</th>
<th>3D-CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Target volume coverage (81 Gy)</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>% of rectal wall – 75 Gy</td>
<td>9%</td>
<td>13%</td>
</tr>
</tbody>
</table>

IMRT reduced late g – II Rectal morbidity

Zelefsky MJ et al, IJROBP, 2008, 70, 1124
Late GI effect

Prospective IMRT studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient no.</th>
<th>Dose fraction</th>
<th>FU (mo)</th>
<th>Grade II morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Meerleer et al, 2007</td>
<td>133</td>
<td>74 – 76 Gy</td>
<td>36</td>
<td>17 %</td>
</tr>
<tr>
<td>Vora et al, 2007</td>
<td>145</td>
<td>75.6 Gy</td>
<td>48</td>
<td>23 %</td>
</tr>
</tbody>
</table>

Cahlon O et al Semin Radiate Oncol 2008, 18, 48
9. Hypofraction

**Late GI effect**

Prospective hypofractionation studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient no.</th>
<th>Dose fraction</th>
<th>NTD$_{2\text{Gy}}$ ($\alpha/\beta - 1.5$)</th>
<th>Grade II morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kupelian, 2007</td>
<td>770</td>
<td>70 Gy / 2.5 Gy</td>
<td>80 Gy</td>
<td>4.5 %</td>
</tr>
<tr>
<td>Tsuji, 2005 *</td>
<td>201</td>
<td>66 GyE / 3.3 GyE</td>
<td>90.5 Gy</td>
<td>1 %</td>
</tr>
<tr>
<td>Martin, 2006</td>
<td>92</td>
<td>60 Gy / 3 Gy</td>
<td>77 Gy</td>
<td>2 %</td>
</tr>
<tr>
<td>Madsen, 2007</td>
<td>40</td>
<td>33.5 Gy / 6.7 Gy</td>
<td>78.5 Gy</td>
<td>7.5 %</td>
</tr>
</tbody>
</table>

* C ion, 4f / week, daily CT imaging, daily bladder filling and rectal enema – no ≥ grade III toxicity

Miles EF et al Semin Radiate Oncol 2008, 18, 41
Late GI effect

Late GI morbidity fades with time

**RT + hormones:**
RTOG 8531, 8610, 9202
N=2922, follow up 10.3 years

Short course hormone, neoadjuvant + concurrent shows lesser grade III morbidity

Lawton CA et al, IJROBP, 2008, 70, 437

Karlsdottir H et al, IJROBP, 2008, 70, 1478
Treatment of radiation proctitis: acute

**Amifostine**, s.c & intrarectal, was found to reduce acute rectal morbidity

SynodinouMenegaki M et al, IJROBP, 2002, 64, s268
Singh AK et al IJROBP, 2006, 65, 1018 & 2008,70, 90
Treatment of radiation proctitis: late

1. Sucralfate / steroid enema,
2. Sulfasalazine oral
3. Pentosan-polysulfate, (fibrinolytic anti-inflammatory mucoprotective)
4. Formalin application to the rectal mucosa
5. Laser therapy (Argon, Nd:YAG) Risk: transmural necrosis
6. Butyric acid (short chain fatty acid) enema

Surgical fecal diversion
Treatment of radiation proctitis: late

Animal studies

1. Late radiation intestinal morbidity – stromal accumulation of fibrogenic mediator connective tissue growth factor (CTGF). It acts through Rho/Rho cell signaling pathway
   **Pravastatin** (a statin) inhibits Rho isoprenylation and CTGF. \(^{(1)}\)

2. RT -> endothelial injury through loss of thrombomodulin (TM)
   **Simvastatin** upregulates TM, with protection of endothelium & reduction of late effects. \(^{(2)}\)

---

Treatment of radiation proctitis: late

Hyperbaric oxygen

- Improvements observed for incontinence, diarrhoea, bleeding and pain
- Incontinence and mild bleeding resolve the most

Woo TCS et al, IJROBP, 1997, 39, 690

Rectal ulcer, post RT

After HbO treatment

Nakabayashi M et al, Urol Oncol Semin, 2006, 24, 503
Acute GU effects
Acute GU effects - RTOG grade

Grade I

- Frequency/nocturia twice pre RT
- Dysuria
  - No drugs required

Grade II

- Frequency/nocturia less frequent than hrly
- Dysuria, spasms
  - Needs drugs, occasional narcotics

Grade III

- Frequency/nocturia hourly or more
- Dysuria, pain, spasms - frequent narcotics
- Gross hematuria, needs transfusion
- Catheter for urinary obstruction/clots

Grade IV

- Gross hematuria, needs > 1 transfusion
- Hospitalization for sepsis due to obstruction, ulcer, necrosis of bladder
Acute GU effects

- Acute GU symptoms – appears in 3rd week of RT (frequency, nocturia, urgency, dysuria)
- 60 % require medication

<table>
<thead>
<tr>
<th>Dose (Gy)</th>
<th>Acute GU morbidity</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade III</td>
<td>Grade IV</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>3%</td>
<td>1%</td>
<td></td>
</tr>
<tr>
<td>78</td>
<td>4%</td>
<td>1%</td>
<td></td>
</tr>
</tbody>
</table>

Acute morbidity correlates with percentage of bladder treated to ≥ 70 Gy

Storey MR et al et al, IJROBP, 2000, 48,635
Acute GU effects

N 114, IMRT, 74 – 78 Gy, Belgium

<table>
<thead>
<tr>
<th>Grade</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>G 0</td>
<td>10 %</td>
</tr>
<tr>
<td>G I</td>
<td>47 %</td>
</tr>
<tr>
<td>G II</td>
<td>36 %</td>
</tr>
<tr>
<td>G III</td>
<td>7 %</td>
</tr>
</tbody>
</table>

1. More pronounced than GI morbidity
2. Higher with increasing dose
3. Cause- urethral/bladder neck inflammation

De Meerleer G et al, IJROBP, 2004, 60, 777
**Acute GU effects**

**3DOG / RTOG 9406, 68.4 / 73.8 Gy**

Acute GU effect increases with neo adjuvant + concurrent hormone therapy

Michalski JM et al, IJROBP, 2000, 46, 391
Late GU effects
Late GU effects - RTOG grade

Grade I
- Slight epithelial atrophy
- Minor telangiectasia
- Microscopic hematuria

Grade II
- Moderate frequency
- Generalized telangiectasia
- Intermittent microscopic hematuria

Grade III
- Severe frequency & dysuria
- Generalized telangiectasia (petechiae)
- Frequent hematuria
- Reduction in bladder capacity (<150cc)

Grade IV
- Necrosis
- Bladder capacity <100cc
- Severe hemorrhagic cystitis
Late GU effects

RTOG 7506, 7706, N= 1020 patients, hospitalization due to chronic urinary sequelae (cystitis, hematuria, urethral stricture, bladder contracture) occurred in 7.3% patients.

Surgical intervention due to urinary toxicity - in 0.5%.

The commonest late urinary complication was urethral stricture occurring mostly in patients with previous TURP.
Late GU effects

Prospective studies

Bladder, urethral morbidities ≥ grade 2 do not show any consistent increase in incidence at escalated dose compared to standard dose.
Late GU effects

Higher dose no increase in morbidity – 3DCRT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>GyE 1</th>
<th>GyE 2</th>
<th>Percentage 1</th>
<th>Percentage 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MGH Boston, Loma Linda</td>
<td>70.2</td>
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<td>Zietman AL et al, JAMA, 294, 1233, 2005</td>
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<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Dutch multicentre</td>
<td>68</td>
<td>78</td>
<td>41%</td>
<td>39%</td>
</tr>
<tr>
<td>Peeters et al JCO, 2006, 24, 1990</td>
<td></td>
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</tr>
</tbody>
</table>

Prospective randomized studies
Late GU effects

N 1571, T1-T3, 3DCRT / IMRT, 68 – 81 Gy (MSKCC)

At 10 years ≥ grade II – 15%
81 Gy - 20%
< 81 Gy - 12%

Occurrence of acute GU morbidity ≥2 significantly increased late GU toxicity

Zelefsky MJ et al, IJROBP, 2008, 70, 1124
Late GU effects

N= 331, 3DCRT - 75.6Gy (Michigan)

Strong predictors for chronic GU toxicity
1. Acute urinary toxicity
2. Bladder dose-volume

Erectile tissue dysfunction (ED)
Erectile tissue dysfunction

There is a fall in potency after curative RT

N=743, post RT likelihood of potency loss 60%

Zelefsky MJ et al, Cancer, 1999, 85, 2460

N=268, 3DCRT, 68 to 78 Gy
3 years post RT only 38% had potency

Erectile tissue dysfunction

Cause of ED: RT to penile bulb & vascular tissue (CC)

MRC RT01: Penile Bulb - D50 ≥ 60 Gy, significant risk of Erectile dysfunction

Stephen M et al., IJROBP, 2005, 63, S126,

McLaughlin PW et al., IJROBP, 2005, 61, 20-31, Michigan
Erectile tissue dysfunction

N-10, IMRT 80 Gy, Vessel sparing protocol, MRI & CT

Time-of-flight MRI angio to define Int.pud.artery(IPA)

- \( D_{50} \) for IPA 35 Gy
- 70% of PB 9.7 Gy

McLaughlin PW et al., IJROBP, 61, 20-31, 2005, Michigan
Thank You